Title: Effectiveness of Orally Dosed Emergency Contraception in Obese Women – UPA

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This randomized cross-over study was conducted at Oregon Health & Science University (OHSU) in Portland, OR, USA and Eastern Virginia Medical School (EVMS) Norfolk, VA, USA. The Institutional Review Board (IRB) at OHSU and EVMS approved the study protocol. We recruited healthy women 18-35 years old who with regular menstrual cycles (21-35 days) with a BMI at or greater than 30 kg/m^2 and a weight of 176 lbs or more (80 kg). In addition to this, 12 women with a BMI <25 kg/m^2 were also recruited as controls. All subjects were required not to be at risk for pregnancy (e.g. abstinent, non-hormonal method of birth control, or non-sperm producing partner). Major exclusion criteria obtained via participant report, review of medical records, and clinical exam included sensitivity or allergy to UPA; treatment for infertility; metabolic disorders including uncontrolled thyroid dysfunction or polycystic ovarian syndrome or clinical evidence of androgen excess; a screening serum progesterone level <3 ng/mL; impaired liver or renal function; actively seeking or involved in a weight loss program (weight stable) or prior bariatric surgery; pregnancy or seeking pregnancy; breastfeeding; recent (8 weeks) use of hormonal contraception; smoking, vaping, or chronic marijuana use.

After an initial telephone screening, participants completed an in-person screening visit to collect baseline demographic and health information and a serum progesterone level during luteal phase to confirm ovulatory status (progesterone level ≥3 ng/mL), an inclusion criterion for participation. All participants completed written informed consent prior to any study procedures. The study was conducted over three menstrual cycles, Cycles 1 and 3 were treatment cycles interspersed by Cycle 2, a washout cycle. For the normal BMI control group, participants only underwent one treatment cycle. We did not have participants undergo a baseline cycle with ultrasound and hormone monitoring. Participants could request to space Cycle 1 and 3 longer than 1 cycle for personal scheduling conflicts or study staff had participants delay an additional cycle, if menses delay occurred in Cycle 2 but if spacing was longer than 3 months, then rescreening would need to take place (n = 0). Additionally, our study procedures overlapped with the first

six months of the COVID-19 pandemic resulting in suspended procedures for several months as directed by state and institutional mandates.

Our monitoring procedures were as follows: day 6-8 of treatment cycles 1 and 3, participants came in every other day until a dominant follicle measuring ≥15 mm in at least one dimension was visualized.[7,9,10] These visits consisted of follicular activity monitoring via transvaginal ultrasound and blood sampling for progesterone (P4), estradiol (E2), and luteinizing hormone (LH). After a pregnancy test was performed and the results were negative, the cohort with a BMI at or greater than 30 kg/m^2 and a weight of 176 lbs were randomized to UPA 30 mg or 60 mg for Cycle 1 and then the other dose for Cycle 3. The OHSU research pharmacy maintained the computer-generated randomization scheme and kept treatment assignments in a locked database. Those in the control group, received a single dose of UPA (30 mg) during Cycle 1 only. Following dosing, all subjects were seen daily for blood sampling and ultrasound monitoring until evidence of follicle rupture (>50% reduction of mean size or complete disappearance of follicle) or for up to 7 days.[4,7,9,10]

Participants could volunteer for additional study procedures to obtain PK samples. PK parameters were obtained via serum samples through an indwelling catheter. We obtained samples during treatment cycles at the time of dosing at 0.5, 2, 1.5, 2, 3, 4, 24, 48, 72, 96, and 120 hours. PK parameters were generated by noncompartmental methods using WinNonLin (Pharsight, Mountain View, CA). Cmax and time to maximum Cmax are observed values. Area under the curve (AUC) was calculated from Time 0 to 120 hr (AUC0-120) using the linear trapezoidal rule and then extrapolated to infinity which provide a more accurate calculation of drug clearance (Rowland 1980). Drug half-life (t1/2), oral clearance (CL), and volume of distribution (VD) will be generated using standard pharmacokinetic calculations (t1/2 =0.693/λz where λz is the terminal elimination rate constant; CL=dose/AUC0-infinity; VD=CL// λz). Descriptive statistics will be generated for each parameter [mean (standard deviation)], concentration-time curves will be generated for all of the doses and their respective BMI groups. Depending on the

normality of the data, parametric or nonparametric testing will be performed for each parameter between the normal and obese BMI EC 30 mg groups and paired statistics will be utilized to compare obese BMI 30 versus 60 mg UPA groups.

Our primary outcome was the difference in the proportion of subjects with no follicle rupture 5 days post-dosing (yes/no) between dosing groups (30 mg vs 60 mg) in the BMI at or greater than 30 kg/m^2 cohort. Our main secondary outcome was the timing (day) of follicle rupture between dosing groups in the BMI at or greater than 30 kg/m^2 cohort. We also calculated these outcomes for our control group and descriptively compared it with the BMI at or greater than 30 kg/m^2 cohort. If the date of follicle rupture was unclear by ultrasound imaging (e.g. collapse was seen but reduction of size was <50%), we utilized serum hormone levels to adjudicated day of rupture. Two investigators independently reviewed these cycles while being masked to dosing and if a disagreement occurred, a third investigator was engaged.

Hormone assays were performed by The Endocrine Technologies Core (ETC) at the Oregon National Primate Research Center (ONPRC, Beaverton, Oregon (https://www.ohsu.edu/onprc/endocrine-technologies-core) performed the hormone, UPA, and Monodemethyl-UPA assays. Serum E2, P4, and LH were analyzed by a Roche Cobas e411 chemiluminescence-based automated immunoassay platform (Roche Diagnostics, Indianapolis, IN). The sensitivities of the E2, P, and LH assays for the Roche e411 are 5 pg/ml, 0.050 ng/ml, and 0.1 mIU/ml, respectively. The intra- and inter-assay variation with the Roche e411 in the ETC is consistently less than 7% for all assays. Quality control sample analyses were repeated prior to each assay run. Serum ulipristal acetate (UPA) and *N*-monodemethylated (NDM)-UPA concentrations were simultaneously determined by ultra-high performance liquid chromatography-heated electrospray ionization-tandem triple quadrupole mass spectrometry (LC-MS/MS) on a Shimadzu Nexera-LCMS-8050 instrument (Shimadzu Scientific, Kyoto, Japan). The lower limit of quantification for both UPA and NDM-UPA was 0.19 ng/ml. Samples with concentrations above 200 ng/ml were re-analyzed after 1:5 dilution in 0 standard. Data processing and analysis were performed using

LabSolutions Software, V5.72 (Shimadzu). Intra-assay coefficient of variation (CV) for UPA ranged from 3.2-14.3% with an inter-assay CV of 6.3% (n=5 assays). Intra-assay CV for NDM-UPA ranged from 2.9-7.4% with an inter-assay CV of 4.5% (n=5 assays). Accuracy was 104.8% for UPA and 106.5% for NDM-UPA. The UPA and NDM-UPA assays were developed and validated largely following FDA guidelines for bioanalytical method validation [FDA Bioanalytical Method Validation Guidance for Industry, 2018] by assessing specificity, stability, precision, accuracy, extraction efficiency (recovery), calibration curve, sensitivity, and reproducibility.